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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,256	12/18/2003	James E. Dahlberg	FORS-08497	1902

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EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/740,256	DAHLBERG ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-34,36 and 39-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34,36 and 39-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/23/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

Status of the Claims

Claims 32-34, 36, and 39-82 are pending. The following Office Action is in response to Applicant's response dated March 23, 2006.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the

undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Figures 12, 24, and 25, respectively contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed August 30, 2002. Applicant should provide a substitute sequence listing and a CRF that include those sequences.

With regard to Applicants' response, the M.P.E.P. clearly states, "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims" (§ 1.821(d)). Sequences presented in figures are included as part of the text of the disclosure. It must be clear from the *figure* which sequence identifier corresponds to the appropriate sequence.

Appropriate correction is required.

Specification

The previous objection of the abstract of the disclosure is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 32 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 57, and all claims dependent thereof, are indefinite because the phrase --wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion **can** hybridize to each other-- renders the claim language unclear as to whether the limitation(s) set forth are part of the claimed invention. In other words, it is unclear whether hybridization of the first portion and said second portion of the second region is an *essential* limitation to the claimed method.

Claim Rejections - 35 USC § 103

The previous rejections of claims over Bagwell or Nazarenko in view of the applied secondary references are withdrawn in view of Applicants' amendments.

The following rejections are necessitated by Applicants' amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 32, 33, 39, 48-50, 51, 52, 54, 55, 58, 60, 62, 63, 72-76, 78, 79, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (U.S. 5,215,899) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

With regard to Claims 32 and 57, Dattagupta et al. teach a method for analyzing RNA (Figure 4; Columns 12,13, Examples 1-3, for example) comprising: a) contacting RNA with an unlabeled probe to form an RNA detection structure (Figure 1; Column 12, Lines 45-60, for example), wherein said probe comprises a first region that is complementary to said RNA and a second region that is not complementary to said RNA (Figures 1,2; Column 12, Lines 30-45, for example), wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion can hybridize to each other when said probe is hybridized to said RNA (Figures 1,2; Column 12, Lines 30-45, for example); and b) detecting said RNA detection structure (Column 12, Lines 60-67, for example) through an amplification reaction (Column 9, Lines 1-20, for example). Dattagupta does not expressly disclose microRNA detection.

Lau et al. disclose two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (Abstract; Table 1, for

example), an obvious structurally equivalent species of the genus molecule RNA. Lau further teaches the detection of miRNAs (Figure 3, for example) as well as the motivation to study these molecules, as their abundance implies that they function in a variety of regulatory pathways.

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to apply the RNA detection methods of Dattagupta to microRNA, an obvious structurally equivalent species of the genus molecule RNA since Lau suggests the detection and further study of these molecules because their abundance implies that they function in a variety of regulatory pathways.

With regard to Claims 33, 48-50, 62, and 72-74 Lau expressly teaches quantitating microRNA and distinguishing unique microRNA from another nucleic acid in a cell lysate sample (Figure 3, for example).

With regard to Claims 39 and 63, Dattagupta expressly teaches incorporation of labeled nucleotide analogs into the probe (Column 12, Lines 60-65, for example).

With regard to Claims 51, 52, 75, and 76 Lau expressly teaches a plurality of different miRNAs 21-22 nucleotides in length (Figure 3; Page 860, Table 1, for example).

With regard to Claims 54 and 78, Lau expressly teaches Let-7 miRNA (Abstract; Table 1, for example).

With regard to Claims 55 and 79, Dattagupta expressly teaches incorporation of nucleotide analogs (Column 12, Lines 60-65, for example).

With regard to Claims 58 and 60, Dattagupta expressly teaches target amplification with signal generating nucleotides (Column 12, Lines 55-67, for example).

With regard to Claims 81 and 82, Dattagupta expressly teaches formation of a dimer structure that comprises two probes that function equivalent to the hairpin structure of Figure 2 (Figure 3; Column 4, Lines 5-25, for example). This teaching encompasses further contacting the RNA detection structure with a second unlabeled probe, wherein said second unlabeled probe comprises a first region that is complementary to the nucleic acid sample and a second region that is not complementary to the nucleic acid sample.

2. Claims 34 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (U.S. 5,215,899) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862), in further view of Prudent et al. (U.S. 5,985,557).

With regard to Claims 34 and 61, the methods of Dattagupta et al. have been outlined in above rejections. Dattagupta does not specifically disclose forming an invasive cleavage structure, cleaving said invasive cleavage structure, and detecting the cleavage of said invasive cleavage structure.

Prudent et al. disclose forming an invasive cleavage structure (Figures 16A-E, Figure 29, for example), cleaving said invasive cleavage structure (Columns 31-39,

Example III, for example), and detecting the cleavage of said invasive cleavage structure(Columns 31-39, Example III, for example). They further disclose that the invader-directed or "invasive" cleavage assay is useful in the detection and quantification of individual variants or alleles in a mixed sample population (Column 38, Lines 15-60).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Dattagupta et al. further comprising detection using an invasive cleavage assay. The motivation to do so, provided by Prudent et al., would have been to detect and quantify individual variants or alleles in a mixed sample population. At the time of invention, the disclosure of Prudent et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

3. Claims 36, 44-47, 59, and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (U.S. 5,215,899) in view of Morris et al. ("Rapid reverse transcription-PCR detection of hepatitis C virus RNA in serum by using the TaqMan fluorogenic detection system J Clin Microbiol. 1996 Dec;34(12):2933-6).

With regard to Claims 36, 44-47, 59, and 68-71, the methods of Dattagupta et al. have been outlined in above rejections. Dattagupta does not specifically disclose the incorporation of TaqMan PCR.

Morris et al. expressly teach TaqMan RT-PCR encompassing the limitations set forth in the above claims (Figure 1; Page 2934, Materials and Methods, RT-PCR, for example). Furthermore, they teach that in the TaqMan assay postamplification manipulations are reduced therefore offering significant time savings.

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate the TaqMan PCR assay disclosed by Morris into the methods of Dattagupta since Morris suggests such a modification for significant time savings.

4. Claims 40-43, 53, 64-67, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (U.S. 5,215,899) in view of Marras et al. "Multiplex detection of single-nucleotide variations using molecular beacons" Genet Anal. 1999 Feb;14(5-6):151-6).

With regard to Claims 40-43, 53, 64-67, and 77, the methods of Dattagupta et al. have been outlined in above rejections. Dattagupta does not specifically disclose the incorporation of FRET enabled molecular beacons to distinguish nucleotide polymorphisms.

Marras et al. expressly teaches detection of single-nucleotide variants (Page 154, Column 2, for example) through the incorporation of FRET enabled molecular

beacons (Figure 1; Page 152, Column 2, for example). Furthermore, Marras teaches that molecular beacons are uniquely suited for the detection of single-nucleotide variants because they their targets with higher specificity the conventional oligonucleotide probes (Page 152, Column 1, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate the FRET enabled molecular beacons disclosed by Marra into the methods of Dattagupta since Morris suggests such a modification because molecular beacons detect polymorphisms with higher specificity than conventional oligonucleotide probes.

5. Claims 56 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (U.S. 5,215,899) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862), in further view of Hyldig-Nielsin et al. (U.S. 5,985,563).

With regard to Claim 56 and 61, the methods of Dattagupta et al. have been outlined in above rejections. Dattagupta does not specifically disclose the use of peptide nucleic acids (PNAs).

Hyldig-Nielsin et al. disclose an assay using PNA probes (Column 17, Lines 30-45; Columns 19,20, Example 1, for example). They further disclose that PNAs have a higher thermal instability of mismatching bases whereby PNAs exhibit a greater

specificity for their complementary nucleic acids than traditionally used nucleic acid probes (Column 2, Lines 40-55).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Dattagupta et al. further comprising detection using PNA probes. The motivation to do so, provided by Hyldig-Nielsin et al., would have been the fact that PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes. At the time of invention, the disclosure of Hyldig-Nielsin et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

Conclusion

Claims 32-34, 36, and 39-82 are rejected. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Dattagupta (EP 0 427 073 A2)

Lane et al. (U.S. 5,770,365)

Stull et al. (U.S. 6,025,133)

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/23/06

Christopher M. Babic
Patent Examiner
AU 1637

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
5/23/06

Notice to Comply	Application No.	Applicant(s)	
	Examiner: Christopher M. Babic	Art Unit: 1637	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1; 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See Office Action

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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